SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS

1 GENERAL INFORMATION

Device Generic Name:	Cardiac Resynchronization Therapy – Defibrillators (CRT-Ds)
Device Trade Name:	CONTAK CD Model 1823; CONTAK CD 2 Models H115 and H119; RENEWAL Model H135; and RENEWAL 3 Models H170, H175, H177 and H179
Applicant's Name and Address:	GUIDANT Corporation, Cardiac Rhythm Management 4100 Hamline Avenue North St. Paul, Minnesota 55112-5798
Date of Panel Recommendation:	July 28, 2004
PMA Number:	P010012/S026
Date of Notice of Approval to Applicant:	September 14, 2004

2 INDICATIONS AND USAGE

Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with moderate to severe heart failure (NYHA III/IV) who remain symptomatic despite stable, optimal heart failure drug therapy, and have left ventricular dysfunction (EF ≤ 35%) and QRS duration ≥ 120 ms.

3 CLINICAL OUTCOMES

Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) have demonstrated the following outcomes in the indicated population specified above:

- Reduction in risk of all-cause mortality or first hospitalization, where a hospitalization is defined as either:
  - Care provided at a hospital for any reason in which the duration is associated with a date change, or
  - Use of intravenous inotropes and/or vasoactive drugs for a duration > 4 hours (inpatient or outpatient).

  NOTE: Hospitalizations associated with a device implant attempt or re-attempt are excluded.

- Reduction in risk of all-cause mortality

- Reduction of heart failure symptoms

4 CONTRAINDICATIONS

There are no contraindications for these devices.

5 WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Physician's System Guide specific to the device being implanted.

6 DEVICE DESCRIPTION

Reference the Physician's System Guide specific to the pulse generator being implanted.

The CONTAK CD[1], CONTAK CD2[2], CONTAK RENEWAL[3], and CONTAK RENEWAL 3[4] devices provide the same ventricular defibrillation therapy and cardiac resynchronization therapy (biventricular pacing) and have the same Indications for Use. Therefore, the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) clinical trial data (based on CONTAK CD devices) used to support expanding Guidant CRT-D indications to the COMPANION patient population, are also applicable to CONTAK RENEWAL and CONTAK RENEWAL 3 and CONTAK CD2.

The primary difference between CONTAK CD devices and CONTAK RENEWAL/CONTAK RENEWAL 3 devices is that CONTAK CD devices utilize an electrically common RV and LV sensing/pacing circuit whereas CONTAK RENEWAL and CONTAK RENEWAL 3 incorporate an independent RV and LV sensing/pacing circuit.

7 ALTERNATE PRACTICES AND PROCEDURES

Patients who have heart failure are routinely treated with medications. Cardiac resynchronization therapy pacemaker (CRT-P) devices are also available to treat heart failure in patients already receiving optimal medications. Additional medical treatments for heart failure include, but are not limited to, exercise and nutrition programs.

[1] P010012, approved May 2, 2002, http://www.fda.gov/cdrh/pdf/P010012.html
[2] P010012/S004 approved October 7, 2002
[3] P010012/S002, approved December 20, 2002
[4] P010012/S008, approved June 13, 2003

8 MARKETING HISTORY

Guidant CRT-Ds are currently available for commercial distribution in the U.S. and other countries including: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Dominican Republic, Finland, France, Germany, Greece, Guadeloupe, Guyana, Hong Kong, Iceland, India, Indonesia, Ireland, Israel, Italy, Jordan, Kuwait, Lebanon, Liechtenstein, Luxembourg, Malaysia, Martinique, Netherlands, New Caledonia, New Zealand, Norway, Portugal, San Marino, Saudi Arabia, Singapore, Slovenia, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, United Kingdom, and Venezuela. As of March 25, 2004, no Guidant CRT-D products have been removed from the market.

9 POTENTIAL ADVERSE EVENTS

Based on the literature and pulse generator implant experience, the following alphabetical list includes possible adverse events associated with implantation of a cardiac resynchronization therapy system:

- Acceleration of arrhythmias
- Air embolism
- Allergic reaction
- Bleeding
- Cardiac tamponade
- Chronic nerve damage
- Conductor coil fracture
- Death
- Electrolyte Imbalance/Dehydration
- Elevated thresholds
- Erosion/extrusion
- Extracardiac stimulation (e.g., phrenic, diaphragm, chest wall)
- Fibrotic tissue formation (e.g., keloid formation)
- Fluid accumulation
- Formation of hematomas or cysts
- Heart block
- Inability to defibrillate or pace
- Inappropriate therapy (e.g., shocks, ATP, pacing)
- Incomplete lead connection with pulse generator
- Infection
- Lead displacement/dislodgment

- Lead fracture
- Lead insulation breakage or abrasion
- Lead tip deformation and/or breakage
- Local tissue reaction
- Muscle and nerve stimulation
- Myocardial trauma (e.g., cardiac perforation, irritability, injury)
- Myopotential sensing
- Oversensing/undersensing
- Pacemaker-mediated tachycardia
- Pericardial rub, effusion
- Pneumothorax
- Random component failures
- Shunting current or insulating myocardium during defibrillation with internal or external paddles
- Thrombosis/thromboemboli
- Valve damage
- Venous occlusion
- Venous trauma (e.g., perforation, dissection, erosion)

Patients susceptible to frequent shocks despite antiarrhythmic medical management may develop psychologic intolerance to an implantable system that may include the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking

In addition to the implantation of an ICD system, potential adverse events associated with implantation of a coronary venous lead system are listed below in alphabetical order:

- Allergic reaction to contrast media
- Breakage/failure of implant tools
- Coronary venous occlusion
- Coronary venous trauma (e.g., perforation, dissection, erosion)

• Prolonged exposure to fluoroscopic radiation

•Renal failure from contrast media used to visualize coronary veins

10 SUMMARY OF PRE-CLINICAL STUDIES

Guidant's commercially available CONTAK CD system was implanted for the CRT-D device arm of the COMPANION study. The CONTAK CD system was previously tested via non-clinical laboratory testing including bench testing, biocompatibility evaluation and animal studies. Device design and system compatibility involved verification and validation of the system. The test results were previously found acceptable[5].

The COMPANION data gathered with CONTAK CD is also applicable to all Guidant CRT-Ds that are commercially available at the date of this approval order. Design differences between CONTAK CD and subsequent generation CRT-D devices were supported by bench and/or clinical data in the following submissions: CONTAK CD2 Models H115 and H119[6]; RENEWAL Model H135, where Guidant first introduced independent RV and LV pacing outputs, justified the applicability of existing CONTAK CD clinical data to RENEWAL, and provided additional Holter data to verify the independent outputs[7]; and RENEWAL 3 Models H170, H175, H177 and H179[8].

11 SUMMARY OF COMPANION CLINICAL STUDY

The COMPANION clinical study was designed to determine whether combined all-cause mortality or first hospitalization in heart failure patients receiving optimal pharmacologic therapy (OPT) can be reduced by combining OPT and 1) biventricular pacing therapy alone (CRT-P)[9] or 2) biventricular pacing with defibrillation (CRT-D). All-cause mortality or first hospitalization (time to first event) analyzed from the time of randomization, was the primary endpoint of the study.

Trial objectives included establishing that OPT combined with biventricular pacing with defibrillation [CONTAK CD] is superior to OPT alone in improving exercise performance (Sub-study)[10], reducing combined all-cause mortality or first hospitalization (Primary endpoint), reducing cardiac morbidity (Secondary endpoint) and reducing all-cause mortality alone (Secondary endpoint).

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[5] P010012, approved May 2, 2002, http://www.fda.gov/cdrh/pdf/P010012.html

[6] P010012/S004 approved October 7, 2002

[7] P010012/S002, approved December 20, 2002

[8] P010012/S008, approved June 13, 2003

[9] Guidant's CRT-P devices were not reviewed as part of this submission and are not part this approval.

[10] The exercise performance substudy was reviewed previously (P030005, approved January 26, 2004, http://www.fda.gov/cdrh/pdf3/p030005.html) and is not discussed in detail in this document.

The COMPANION clinical study began January 20, 2000 and was conducted at 128 centers within the United States. The COMPANION trial utilized a Steering Committee, Data Safety Monitoring Board (DSMB), and Morbidity and Mortality Committee for study conduct, safety, and event adjudication respectively. The study was monitored using a sequential design and on November 18, 2002, after review of the data by the Data Safety and Monitoring Board, enrollment in the study was stopped. The CRT-D arm of the trial had reached the target number of events for the combined primary all-cause mortality or first hospitalization endpoint, as well as the secondary all-cause mortality endpoint. All effectiveness follow-ups ended by December 1, 2002.

11.1 STUDY DESIGN

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Study was a prospective, open-label, randomized, controlled, multi-center, unblinded study which was conducted at 128 sites and enrolled a total of 1638 patients, of which 1520 were randomized. Patients were randomly assigned 1:2:2 to receive optimal pharmacological therapy (OPT, 308 patients) or a cardiac resynchronization therapy pacemaker (CRT-P, 617 patients) or a cardiac resynchronization therapy pacemaker with defibrillator (CRT-D, 595 patients). This summary focuses on data and analyses for the CRT-D and OPT groups only.

Randomization was stratified by centers and by beta-blocker use to assure proper balance between the treatment groups within each center. Each randomized patient remained counted as a member of the original randomization assignment (intention-to-treat) regardless of subsequent crossover or protocol adherence.

Eligible patients were also enrolled in a sub-study designed to measure improvement in exercise performance in patients randomized to CRT (CRT-P and CRT-D pooled data) therapy compared to OPT[11].

11.1.1 ENDPOINTS

This summary focuses on the CRT-D vs. OPT contrast, providing evidence of safety and effectiveness for Guidant CRT-Ds in the COMPANION patient population. The clinical data and analyses herein address the following study endpoints for all patients randomized to CRT-D and OPT.

11.1.1.1 PRIMARY ENDPOINT

The primary endpoint was a composite consisting of all-cause mortality or first hospitalization (time to first event) as analyzed from the date of randomization on an

[11] The exercise performance substudy was reviewed previously (P030005, approved January 26, 2004, http://www.fda.gov/cdrh/pdf3/p030005.html) and is not discussed in detail in this document.

intention-to-treat basis. The study was designed to demonstrate a 25% relative reduction with CRT-D when compared to an estimated 40% annual rate in the OPT cohort. All-cause mortality was defined as death from any cause. Hospitalization is defined below:

Qualifying Duration for Hospitalization

The intent behind hospitalization was to capture inpatient hospitalizations that were of sufficient duration to enter into a composite with all-cause mortality. Thus, hospitalization was defined as care provided at a hospital in which hospital admission and discharge occurred on separate dates. Patients excluded from this definition were those who received care at a hospital, but were discharged on the same day as admission. In addition to hospitalizations, the use of intravenous inotropes or vasoactive agents for a duration of greater than four hours was also considered to be of significant importance to be treated as an instance of hospitalization.

Hospitalizations Related to the Implant Procedure

Hospitalizations associated with device implant (initial and reattempted for unsuccessful initial implant) were not considered to be an event for evaluating the primary endpoint. Similarly, hospitalizations associated with elective implant of devices (i.e., absence of an electrophysiological indication or an ongoing hospitalization requiring intravenous therapy) in the OPT cohort also were not considered to be a primary endpoint event. Surgical revisions of a previous implanted system did count as a primary endpoint event if the revision was of a sufficient duration to result in different admission and discharge dates.

11.1.1.2 SECONDARY ENDPOINTS

All-cause mortality: The all-cause mortality (death from any cause) endpoint was designed to show a 25% reduction in mortality in the CRT-D arm from an OPT annual mortality rate of 24%. Difference in mortality was determined by contrasting patients randomized to CRT-D in addition to OPT versus patients randomized to OPT alone.

Cardiac morbidity: Cardiac morbidity was defined as a hospitalization for one or more of the following events:

- Worsening heart failure resulting in use of intravenous vasoactive or inotropic therapy exceeding four hours
- Mechanical respiratory or cardiac support
- Any cardiac surgery, including heart transplant
- Resuscitated cardiac arrest or sustained ventricular tachycardia requiring intervention (e.g., chest thump, external cardioversion, or external defibrillation)
- Hospitalization for acute decompensation of heart failure

- Hospitalization that results in death from cardiac causes
- Significant device-related events resulting in
  - Permanent disability
  - Hospitalization for pending death or permanent disability

11.1.2 SAFETY

Adverse events were reported and presented in this document (See 11.4).

CRT-D system-related complication-free rate was an additional analysis and was determined by measuring complications related to any of the implanted components or their associated implant procedure in those patients who were successfully implanted with the CRT-D system.

11.1.3 INCLUSION CRITERIA

The study population consisted of patients with moderate to severe heart failure, New York Heart Association Classification III or IV, left ventricular ejection fraction $\leq$35%, and QRS width $\geq$120 ms due to ischemic or non-ischemic cardiomyopathy.

All patients were required to have been treated with a stable dose of beta-blocker, angiotensin converting enzyme (ACE) inhibitor or Angiotensin Receptor Blocker (ARB), diuretic, and aldosterone antagonist. A stable dose was defined as 30 days for all drugs except beta-blocker, which required 90 days stabilization from last up titration prior to randomization. Diuretic dosage could be adjusted any time by the investigator using medical discretion.

Patients enrolled in the study were required to meet the following inclusion criteria:

- Moderate or severe heart failure, defined as symptomatic heart failure for at least six months with NYHA class III or IV symptoms at the time of enrollment, and at least one of the following events in the previous 12 months:
  - Hospitalization for heart failure management
  - Outpatient visit in which intravenous (IV) inotropes or vasoactive infusion were administered continuously for at least 4 hours
  - Emergency room visit of at least twelve hours duration in which IV heart failure medications were administered (including diuretics)
- QRS $\geq$120 ms and PR interval >150 ms from any two leads of a 12 lead ECG
- Left ventricular ejection fraction $\leq$35%
- Left ventricular end diastolic dimension $\geq$60mm (required only if LVEF measured by echo) or >3.0cm/m^2 [The cm/m^2 is calculated by LVEDD (in cm) divided by BSA (body surface area)]
- Age $\geq$18 years
- Optimal pharmacologic therapy for heart failure (beta-blocker, ACE inhibitor, diuretics, and spironolactone)

11.1.4 EXCLUSION CRITERIA

Patients were excluded from the investigation if they met any of the following criteria:

- Unable or unwilling to undergo device implant and follow-up testing
- Meet the general indications for an implantable cardioverter defibrillator
- Meet the general indications for anti-bradycardia pacing
- Expected to receive a heart transplant in the next six months
- Chronic, medically refractory atrial tachyarrhythmias
- Unexplained syncope
- Myocardial infarction within 60 days of randomization
- Hospitalization for heart failure or IV inotropic or vasoactive therapy in excess of 4hours in the 30days prior to enrollment
- History of non-compliance with oral heart failure therapy
- Progressive or unstable angina
- Uncontrolled blood pressure: Systolic BP >160mmHg or <85mmHg or diastolic BP >90mmHg
- Patients with a hypersensitivity to 0.7 mg nominal does of dexamethasone acetate
- Surgically uncorrected primary valvular disease
- Coronary artery disease (CAD) in which surgical or percutaneous correction is recent (within 60 days of randomization)
- Women who are pregnant or not using medically acceptable birth control
- Hypertrophic obstructive cardiomyopathy
- Amyloid disease
- Involved in any other investigational studies
- Life expectancy <6 months due to any other medical conditions

11.1.5 FOLLOW-UP SCHEDULE

Enrollment	Initial assessment of patient eligibility; taking of patient history.
Baseline Screening	Special testing*
Randomization	Randomization status (OPT, CRT-P, or CRT-D) was assigned.
Implant	Implant of investigational devices and acute device testing for those randomized to a CRT therapy arm.
Routine Follow-up	Routine evaluation of device function and patient condition at pre-discharge, one week, and one month.
Three- and six-month Visits	Evaluation of randomized therapy with Special Testing* and device function at three and six months after the Post-Recovery Visit.

Quarterly Visits	After the six-month visit, patients were seen for routine evaluation of device function and patient condition.

*Special Testing included a Symptom-Limited Treadmill Test with measurement of oxygen uptake (Peak VO_2), a Six-Minute Walk, Quality of Life (QOL) questionnaire and New York Heart Association Classification.

11.2 GENDER BIAS

Comparable data of gender distribution is not available, due to the fact that there have not been reports on prior studies with designs similar to this study. However, the COMPANION study protocol required all patients to be selected from investigator's general patient population and only to exclude female patients who were pregnant or not using medically acceptable birth control methods, which concurred with the normal practice for conducting clinical trials.

Four hundred and one men (67%) and 194 women (33%) were randomized to receive a CONTAK CD device, while 211 men (68%) and 97 women (32%) were randomized to the control arm (OPT). No statistical difference was found between the CRT-D and OPT groups with respect to gender distribution (p=0.74, t-test).

For the primary endpoint and the secondary all-cause mortality endpoint, Cox proportional-hazard regression models were used to estimate the hazard ratios and 95 percent confidence intervals for therapy effectiveness. In order to determine if therapy effectiveness differed between males and females, gender and the interaction between gender and treatment were assessed within the model.

There is no significant interaction between treatment and gender (p=0.870) with respect to the primary endpoint. This indicates that the effect of treatment (CRT-D) on all-cause mortality or all-cause hospitalization does not differ by gender.

There is no significant interaction between treatment and gender (p=0.790) with respect to all-cause mortality. This indicates that the effect of treatment (CRT-D) on mortality does not differ by gender.

11.3 PATIENT ASSESSMENTS

11.3.1 DEMOGRAPHIC DATA

Baseline patient characteristics are presented in Table 1.

Table 1: Characteristics of Patient Population

Characteristic		OPT (N=308)	CRT-D (N=595)	P-value
Age (years)	Mean +/- SD	66.7 +/- 10.7	65.6 +/- 11.2	0.14
Gender [N (%)]	Female	97 (31.4)	194 (32.6)	0.73
	Male	211 (68.5)	401 (67.3)	
NYHA Classification [N (%)]	Class III	253 (82.1)	512 (86.1)	0.12
	Class IV	55 (17.8)	83 (13.9)	
Ischemic Etiology (%)	Ischemic	58.7	54.6	0.13
	Non-ischemic	41.3	45.4	
LVEF (%)	Mean +/- SD	22.8 +/- 7.2	22.5 +/- 6.8	0.47
Resting Heart Rate (bpm)	Mean +/- SD	72 +/- 12	73 +/- 13	0.37
QRS Width (ms)	Mean +/- SD	156 +/- 24	159 +/- 24	0.09
Conduction Abnormality (%)	LBBB	69.8	72.9	0.21
	Non-specific	21.4	16.8	
	RBBB	8.77	10.2	
Duration of Heart Failure (years)	Mean +/- SD	4.86 +/- 4.41	4.44 +/- 3.83	0.43
Heart Failure Medications [(%)]	Diuretic	94.4	96.6	0.12
	ACE inhibitor or ARB	88.6	89.6	0.66
	Beta Blockers	66.2	67.6	0.69
	Aldosterone Antagonist	54.8	55.1	0.94
	Digoxin	67.2	70.9	0.25

11.3.2 BASELINE MEDICATIONS

Table 2 lists the drugs to which patients were prescribed, as required by protocol, unless contraindicated at the time of randomization. There were no significant differences at baseline or at the last follow up on or before the efficacy follow-up through November 30, 2002. Over 60% of patients had their last efficacy follow-up completed $\geq$ 12 months from randomization.

Table 2: Medication Use at Baseline and Last Follow-up

Medication	CONTAK CD (N BL=595 N FU=582)	OPT (N BL=306 N FU=285)	P-value
Ace inhibitor use (patients, %)			
Baseline/Enrollment	533 (89.6%)	273 (89.2%)	0.87
Last Follow-up	477 (82.0%)	247 (86.7%)	0.08
Amiodarone use (patients, %)			
Baseline/Enrollment	328 (55.1%)	169 (55.2%)	0.98
Last Follow-up	266 (45.7%)	139 (48.8%)	0.40
Beta blocker use (patients, %)			
Baseline/Enrollment	402 (67.6%)	204 (66.7%)	0.79
Last Follow-up	427 (73.4%)	198 (69.5%)	0.23
Digoxin use (patients, %)			
Baseline/Enrollment	422 (70.9%)	207 (67.6%)	0.31
Last Follow-up	399 (68.6%)	192 (67.4%)	0.72
Diuretic use (patients, %)			
Baseline/Enrollment	578 (97.1%)	292 (95.4%)	0.18
Last Follow-up	525 (90.2%)	263 (92.3%)	0.32

11.3.3 PATIENT ACCOUNTABILITY AND FOLLOW-UP DURATION

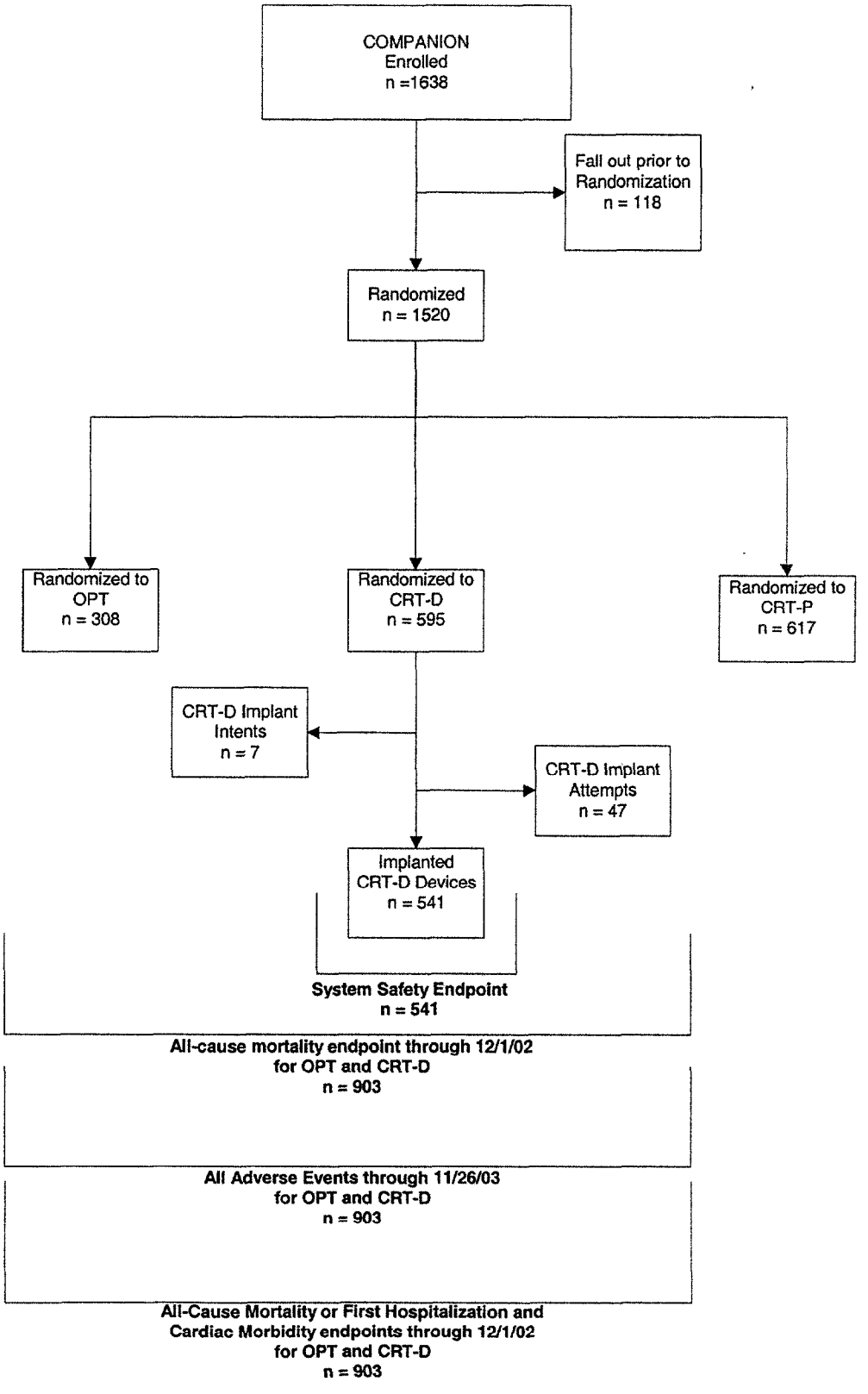
The COMPANION study enrolled 1638 patients, with 1520 patients randomized to a treatment group and one hundred eighteen patients (118) not randomized due to changes in patient condition or consent between time of enrollment and time of randomization, such that the inclusion criteria were no longer satisfied. Of the 1520 patients, 595 were randomized to CRT-D with a mean follow-up of 1.3 years and 308 were randomized to OPT with a mean follow-up of 1.1 years. Figure 1 provides an overview of patient enrollment.

Table 3 gives a summary (by treatment group) of patient disposition over time through 12 months after randomization. This does not account for patients that had a hospitalization or death event that contributed to the primary endpoint or secondary endpoint of all-cause mortality. For events contributing to the primary endpoint or the secondary endpoint of all-cause mortality, please refer to Figure 2 and Figure 3.

Table 3: Patient Follow-up Disposition 12 Months Post Randomization

	CRT-D				OPT			
	# of With-drawn Patients	# of Deceased Patients	(N = 595) # Reached end of study (Nov. 30, 2002)	# of Active Patients at end of time interval	# of With-drawn Patients	# of Deceased Patients	(N = 308) # Reached end of study (Nov. 30, 2002)	# of Active Patients at end of time interval
1 Day - 7 Days	4	3	0	588	6	0	0	302
7 Days - 1 Month	4	3	5	576	10	3	1	288
1 Month - 3 Months	4	15	6	551	11	11	1	265
3 Months - 9 Months	12	28	49	462	26	22	29	188
9 Months - 12 Months	1	12	35	414	11	11	19	147

Figure 1: Study Patient Enrollment and Randomization for CRT-D and OPT.



11.3.4 EVENTS CONTRIBUTING TO PRIMARY ENDPOINT AND SECONDARY ENDPOINT OF ALL-CAUSE MORTALITY

A total of 903 COMPANION patients in the CRT-D (595) and OPT (308) groups were eligible for the primary endpoint. Figure 2 provides patient randomization and status for the primary endpoint and Figure 3 provides patient randomization and status for the secondary mortality endpoint.

Figure 2: CRT-D and OPT Patient Randomization for Primary Endpoint.

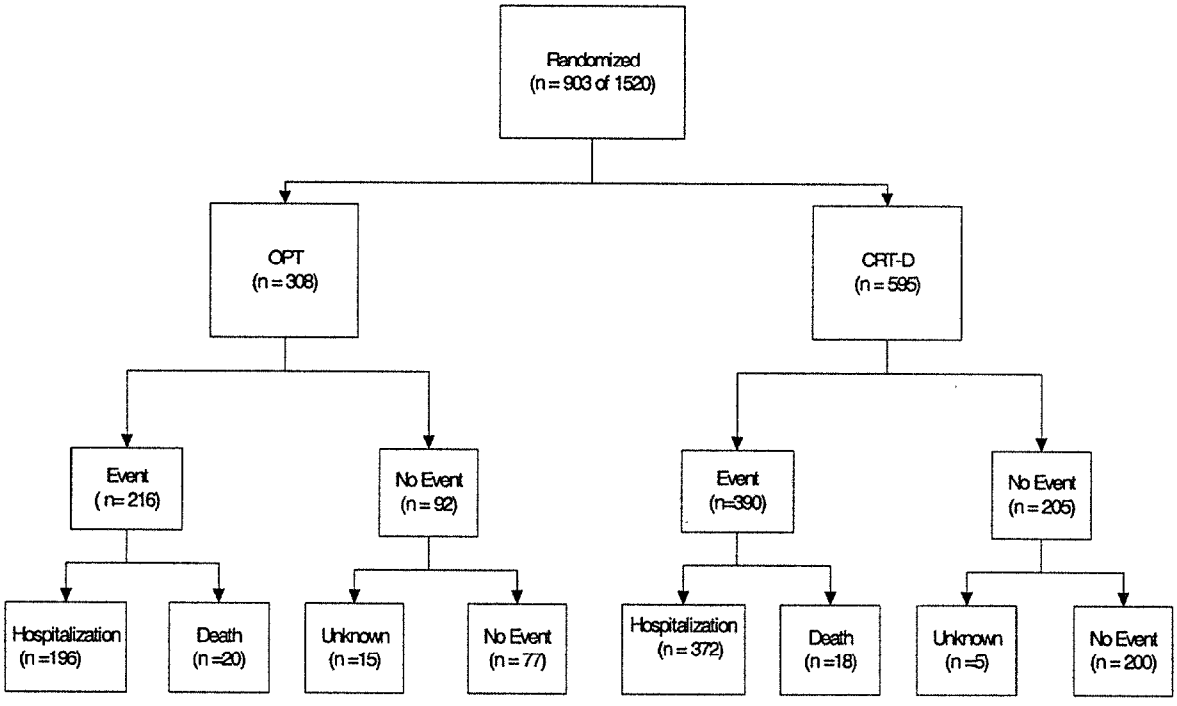
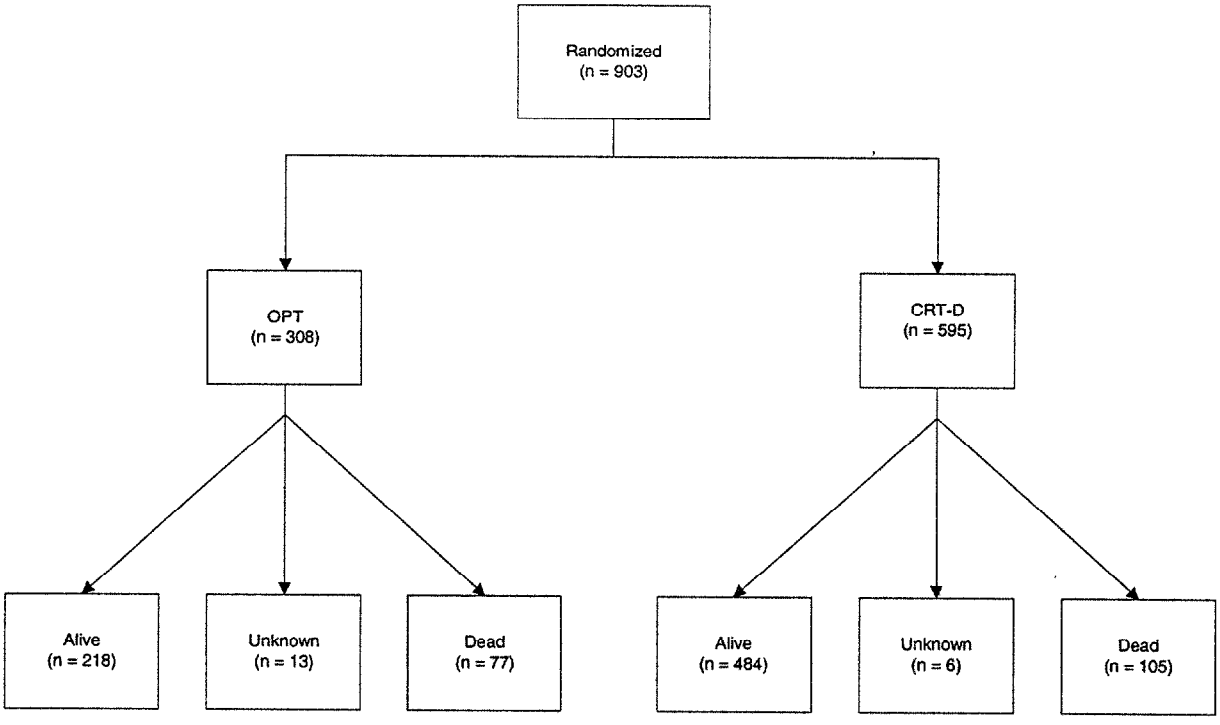


Figure 3: CRT-D and OPT Patient Randomization for Mortality Endpoint.



11.4 OBSERVED ADVERSE EVENTS

Adverse events were defined as any undesirable clinical occurrence, whether it was related to the device or not. Table 4 includes adverse events occurring in the first six months related to the device (pulse generator and leads) and implant procedures (including attempts). Table 5 includes adverse events occurring in the first six months related to patient condition (i.e., worsening heart failure). Adverse events are listed in descending order by total number of patients experiencing the event.

Adverse events related to the device were further reported using two sub-categories based on the nature of the intervention. These events were defined as a complication if the event resulted in invasive intervention, loss of significant device function, and death or permanent disability. An observation was a device-related adverse event that was resolved non-invasively. Forty-nine percent (49%) of CRT-D patients reported a device and/or procedure-related adverse event.

Table 4: Device- and Procedure-Related Adverse Events Occurring During the First Six Months Post Randomization[a] (N = 588)

	Total Events (Patients)	%Complications (Patients)	%Observations (Patients)
Total Device/Procedure Adverse Events	**498 (290)**	**13.1 (77)**	**43.4 (255)**
Post surgical wound discomfort	68 (62)	0.0 (0)	10.5 (62)
Phrenic nerve/diaphragm stimulation	77 (59)	1.4 (8)	9.0 (53)
Brady capture - LV	38 (36)	4.3 (25)	2.2 (13)

	Total Events (Patients)	%Complications (Patients)	%Observations (Patients)
Hematoma	37 (34)	0.3 (2)	5.4 (32)
Inappropriate shock above rate cutoff	26 (24)	0 0 (0)	4.1 (24)
Multiple counting - tachy	22 (17)	0.3 (2)	2.9 (17)
Pocket infection	19 (17)	0.5 (3)	2.6 (15)
Dissection, coronary sinus	15 (15)	0.0 (0)	2.6 (15)
Brady capture - atrium	14 (12)	1.5 (9)	0.5 (3)
Inappropriate shock due to oversensing	11 (11)	0.0 (0)	1.9 (11)
Pneumothorax	10 (10)	1.0 (6)	0.7 (4)
Hypotension	10 (9)	0.2 (1)	1.4 (8)
Brady capture - RV	8 (8)	0.9 (5)	0.5 (3)
Physical trauma	8 (8)	0.2 (1)	1.2 (7)
AV Block - heart block, complete	7 (7)	0.2 (1)	1.0 (6)
Pacemaker-mediated tachycardia (PMT)	7 (6)	0.0 (0)	1.0 (6)
Physiological reaction[b]	6 (6)	0.0 (0)	1.0 (6)
Arrhythmia - atrial fibrillation	5 (5)	0.0 (0)	0.9 (5)
Bleeding/fluid accumulation	5 (5)	0.0 (0)	0.9 (5)
Perforation, coronary venous	5 (5)	0.5 (3)	0.3 (2)
Renal failure	5 (5)	0.0 (0)	0.9 (5)
Thrombosis	5 (5)	0.0 (0)	0.9 (5)
Vascular related	5 (5)	0.0 (0)	0.9 (5)
Oversensing - atrium pace sense	4 (4)	0.3 (2)	0.3 (2)
Allergic reaction	3 (3)	0.0 (0)	0.5 (3)
Congestive heart failure	3 (3)	0.0 (0)	0.5 (3)
Nausea (2), Constipation (1)	3 (3)	0.0 (0)	0.5 (3)
High DFTs - tachy	3 (3)	0.2 (1)	0.3 (2)
Oversensing - ventricle rate - tachy	3 (3)	0.2 (1)	0.3 (2)
Respiratory related	3 (3)	0.2 (1)	0.3 (2)
Ventricular tachycardia	3 (3)	0.2 (1)	0.3 (2)
Cardiac tamponade	2 (2)	0.3 (2)	0.0 (0)
Dyspnea (shortness of breath)	2 (2)	0.0 (0)	0.3 (2)
Electrolyte/lab	2 (2)	0.0 (0)	0.3 (2)
Hemorrhage	2 (2)	0.2 (1)	0.2 (1)
Insulation breach suspected	2 (2)	0.3 (2)	0.0 (0)
Migration of device	2 (2)	0.0 (0)	0.3 (2)
Muscle stimulation	2 (2)	0.0 (0)	0.3 (2)
Myocardial infarction	2 (2)	0.0 (0)	0.3 (2)
Numbness	2 (2)	0.0 (0)	0.3 (2)
Perforation, venous	2 (2)	0.0 (0)	0.3 (2)
Phantom shock	2 (2)	0.0 (0)	0.3 (2)
Undersensing - atrium pace sense - brady	2 (2)	0.2 (1)	0.2 (1)
Altered hemodynamic status	1 (1)	0.0 (0)	0.2 (1)
Arrhythmia	1 (1)	0.0 (0)	0.2 (1)
Arrhythmia - sinus tachycardia	1 (1)	0.0 (0)	0.2 (1)
Bruise	1 (1)	0.0 (0)	0.2 (1)

	Total Events (Patients)	%Complications (Patients)	%Observations (Patients)
Cardiac arrest	1 (1)	0.2 (1)	0.0 (0)
Change in arrhythmia - SVT	1 (1)	0.0 (0)	0.2 (1)
Change in arrhythmia - brady	1 (1)	0.0 (0)	0.2 (1)
Change in arrhythmia - junctional	1 (1)	0.0 (0)	0.2 (1)
Change in physical status	1 (1)	0.0 (0)	0.2 (1)
Chest pain	1 (1)	0.0 (0)	0.2 (1)
Dizziness, cause undetermined	1 (1)	0.0 (0)	0.2 (1)
Edema	1 (1)	0.0 (0)	0.2 (1)
Fatigue	1 (1)	0.0 (0)	0.2 (1)
Febrile	1 (1)	0.0 (0)	0.2 (1)
Unable to urinate	1 (1)	0.0 (0)	0.2 (1)
Helix related (screw tip), broken or stretched	1 (1)	0.2 (1)	0.0 (0)
Hemoglobin drop	1 (1)	0.2 (1)	0.0 (0)
Hypertension	1 (1)	0.0 (0)	0.2 (1)
Infection	1 (1)	0.2 (1)	0.0 (0)
Insulation breech observed	2 (1)	0.2 (1)	0.0 (0)
Malfunction, memory problem	1 (1)	0.2 (1)	0.0 (0)
Materials unretrieved in body	1 (1)	0.2 (1)	0.0 (0)
Pacemaker mediated tachycardia (PMT)	1 (1)	0.0 (0)	0.2 (1)
Pacemaker syndrome	1 (1)	0.0 (0)	0.2 (1)
Pericardial effusion	1 (1)	0.2 (1)	0.0 (0)
Pericarditis	2 (1)	0.0 (0)	0.2 (1)
Placement difficulty, stylet related	1 (1)	0.2 (1)	0.0 (0)
Pleural effusion	1 (1)	0.2 (1)	0.0 (0)
Pleurisy	2 (1)	0.0 (0)	0.2 (1)
Pocket erosion/extrusion	1 (1)	0.2 (1)	0.0 (0)
Anxiety	1 (1)	0.0 (0)	0.2 (1)
Respiratory arrest	1 (1)	0.2 (1)	0.0 (0)
Ventricular fibrillation	1 (1)	0.0 (0)	0.2 (1)

a. Observations and complications may not sum to total because some patient may have events in both categories.
b. Swelling, Rash, and/or Drainage.

Table 5: Patient-Related Six Month Adverse Events

	Total Events (Patients)		% of Patients with Events		Events/Patient Year	
	CRT-D	OPT	CRT-D N=595 Patients	OPT N=308 Patients	CRT-D 281 Years	OPT 134 Years
Total Patient-Related Adverse Events	**1437 (443)**	**625 (207)**	**74.5**	**67.2**	**5.11 (1437)**	**4.66 (625)**
Cardiovascular Related Events	**814 (351)**	**399 (176)**	**59.0**	**57.1**	**2.90 (814)**	**2.98 (399)**
Congestive heart failure[a]	269 (166)	185 (111)	27.9	36.0	0.96 (269)	1.38 (185)

	Total Events (Patients)		% of Patients with Events		Events/Patient Year	
	CRT-D	OPT	CRT-D N=595 Patients	OPT N=308 Patients	CRT-D 281 Years	OPT 134 Years
Chest pain	83 (65)	50 (37)	10.9	12.0	0.30 (83)	0.37 (50)
Supraventricular tachyarrhythmia	69 (56)	11 (11)	9.4	3.6	0.25 (69)	0.08 (11)
Ventricular tachyarrhythmia	66 (51)	16 (15)	8.6	4.9	0.23 (66)	0.12 (16)
Electrolyte/lab	51 (42)	17 (16)	7.1	5.2	0.18 (51)	0.13 (17)
Hypotension	42 (40)	16 (15)	6.7	4.9	0.15 (42)	0.12 (16)
Dizziness, cause undetermined	33 (30)	26 (23)	5.0	7.5	0.12 (33)	0.19 (26)
Renal failure	40 (29)	16 (14)	4.9	4.5	0.14 (40)	0.12 (16)
Fatigue	27 (25)	12 (12)	4.2	3.9	0.10 (27)	0.09 (12)
Bradyarrhythmia	32 (30)	5 (5)	5.0	1.6	0.11 (32)	0.04 (5)
Vascular	14 (11)	11 (10)	1.8	3.2	0.05 (14)	0.08 (11)
Syncope	12 (12)	7 (7)	2.0	2.3	0.04 (12)	0.05 (7)
GI bleed	14 (13)	4 (4)	2.2	1.3	0.05 (14)	0.03 (4)
Arrhythmia	12 (10)	6 (6)	1.7	1.9	0.04 (12)	0.04 (6)
Hypertension	12 (9)	6 (5)	1.5	1.6	0.04 (12)	0.04 (6)
Palpitations	9 (9)	3 (3)	1.5	1.0	0.03 (9)	0.02 (3)
Myocardial infarction	7 (7)	4 (4)	1.2	1.3	0.02 (7)	0.03 (4)
Stroke syndrome or CVA	7 (7)	2 (2)	1.2	0.6	0.02 (7)	0.01 (2)
Deep vein thrombosis	4 (4)	0 (0)	0.7	0.0	0.01 (4)	0.00 (0)
Transient ischemic attack (TIA)	3 (3)	1 (1)	0.5	0.3	0.01 (3)	0.01 (1)
Hematuria	3 (3)	0 (0)	0.5	0.0	0.01 (3)	0.00 (0)
Ischemia	2 (2)	1 (1)	0.3	0.3	0.01 (2)	0.01 (1)
Coagulopathy	2 (2)	0 (0)	0.3	0.0	0.01 (2)	0.00 0(0)
Bleeding/fluid accumulation	1 (1)	0 (0)	0.2	0.0	0.00 (1)	0.00 (0)
Non-cardiovascular Related Events	**623 (293)**	**226 (119)**	**49.2**	**38.6**	**2.22 (623)**	**1.69 (226)**
Respiratory related[b]	130 (108)	53 (41)	18.2	13.3	0.46 (130)	0.40 (53)
GI[c]	124 (95)	30 (24)	16.0	7.8	0.44 (124)	0.22 (30)
Pain	82 (66)	40 (32)	11.1	10.4	0.29 (82)	0.30 (40)
Physiological reaction[d]	76 (61)	20 (18)	10.3	5.8	0.27 (76)	0.15 (20)
Infection	54 (37)	18 (15)	6.20	4.9	0.19 (54)	0.13 (18)
Endocrine	41 (35)	16 (14)	5.9	4.50	0.15 (41)	0.12 (16)
Psychological effects	24 (19)	13 (12)	3.2	3.9	0.09 (24)	0.10 (13)
Change in physical status	20 (18)	9 (9)	3.0	2.9	0.07 (20)	0.07 (9)
Physical trauma	26 (22)	4 (4)	3.7	1.3	0.09 (26)	0.03 (4)
Neurologic	14 (14)	6 (6)	2.4	1.9	0.05 (14)	0.04 (6)
Genitourinary	9 (7)	5 (4)	1.2	1.3	0.03 (9)	0.04 (5)
Cancer, other	5 (5)	6 (5)	0.8	1.6	0.02 (5)	0.04 (6)
Febrile	7 (7)	0 (0)	1.2	0.0	0.02 (7)	0.00 (0)
Respiratory failure	4 (4)	1 (1)	0.7	0.3	0.01 (4)	0.01 (1)
Tumors, growths	1 (1)	2 (2)	0.2	0.6	0.00 (1)	0.01 (2)
Ulceration	2 (1)	2 (2)	0.2	0.6	0.01 (2)	0.01 (2)

	Total Events (Patients)		% of Patients with Events		Events/Patient Year	
	CRT-D	OPT	CRT-D N=595 Patients	OPT N=308 Patients	CRT-D 281 Years	OPT 134 Years
Diabetes complications	2 (2)	0 (0)	0.3	0.0	0.01 (2)	0.00 (0)
Pulmonary embolism	1 (1)	1 (1)	0.2	0.3	0.00 (1)	0.01 (1)
Pneumonia (respiratory infection)	1 (1)	0 (0)	0.2	0.0	0.00 (1)	0.00 (0)

a. Congestive heart failure includes: Congestive heart failure, Dyspnea, Volume overload, Edema, Pulmonary edema, Change in drug therapy.
b. The most frequent three events in this category were upper respiratory infection, bronchitis, and influenza.
c. The most frequent three events in this category were nausea, diarrhea, and abdominal pain.
d. The most frequent three events in this category were swelling, rash, and weight gain.

11.5 DEATHS

There were a total of 182 deaths (77 OPT, 105 CRT-D) that occurred during the trial and recorded through November 30, 2002. Table 6 presents deaths stratified by treatment group.

Table 6: CRT-D and OPT Cause of Death

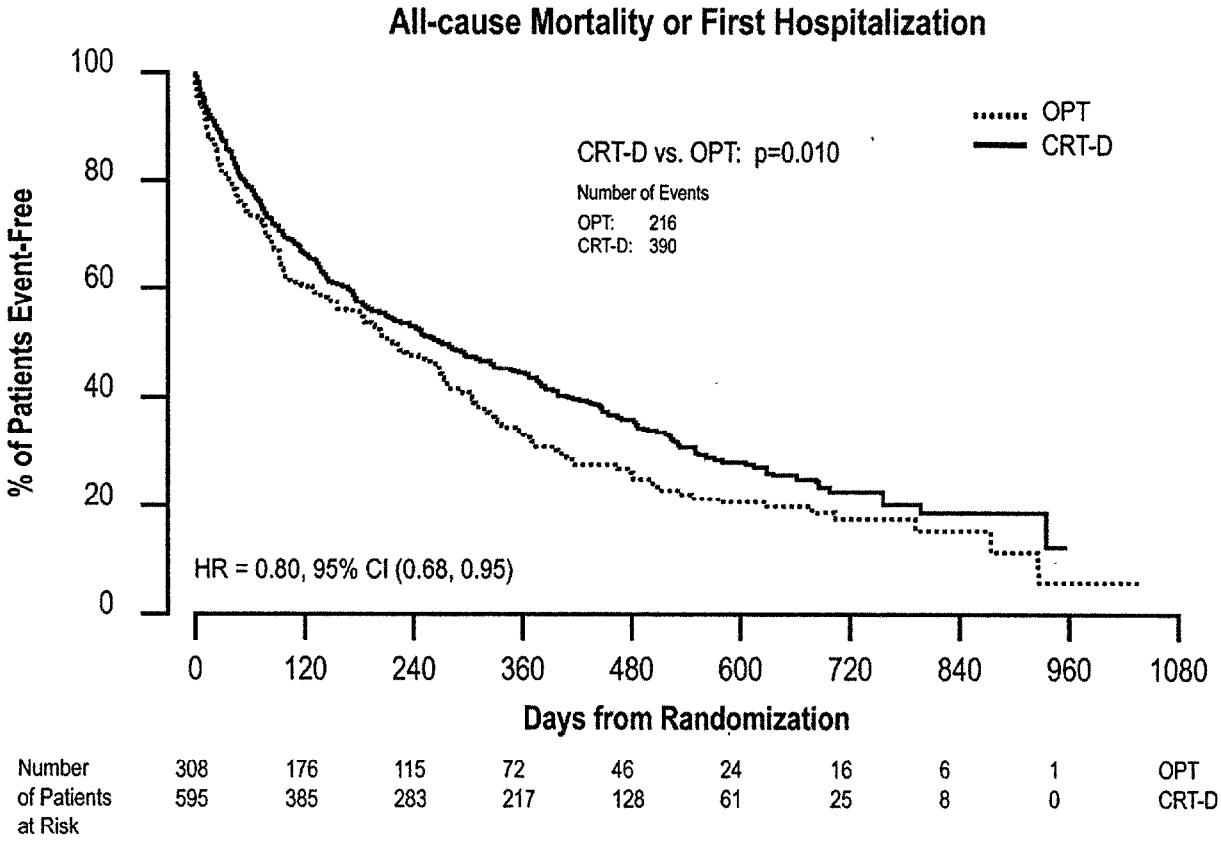
Cause of Death	OPT Arm (N=308)	CRT-D Arm (N=595)	Total (N=903)
Cardiac	58 (18.8%)	76 (12.8%)	134 (14.8%)
Vascular	0 (0.0%)	3 (0.5%)	3 (0.3%)
Non-Cardiac	11 (3.6%)	21 (3.5%)	32 (3.5%)
Unknown/ Unclassified	8 (2.6%)	5 (0.8%)	13 (1.4%)
Total Deaths	**77 (25.0%)**	**105 (17.6%)**	**182 (20.2%)**

11.6 DATA ANALYSIS AND RESULTS

11.6.1 PRIMARY ENDPOINT: ALL-CAUSE MORTALITY OR FIRST HOSPITALIZATION

The Kaplan-Meier curves illustrating the time to all-cause mortality or first hospitalization are shown in Figure 4. There were 216 primary endpoint events observed in the OPT arm and 390 in the CRT-D arm ($p = 0.010$; $p = 0.011$ after adjustment for interim analyses). The median time to first event was 209 days in the OPT group and 269 days in the CRT-D group. The annual event rates for OPT and CRT-D, respectively, were 68.0% and 55.9%, with a hazard ratio of 0.80; 95% CI (0.68, 0.95). This result demonstrated that CRT-D significantly reduced the relative risk of all-cause mortality or first hospitalization by 20% when compared to OPT alone.

Figure 4: Primary Endpoint: All-cause Mortality or First Hospitalization.



In addition to the hazard ratio, point estimates of risk reduction were also calculated (Table 7). These estimates will vary with time from the true treatment effect, and thus should be interpreted with caution.

Table 7: Primary Endpoint Risk Reduction Point Estimates (Overall Hazard Ratio = 0.80; p = 0.010)

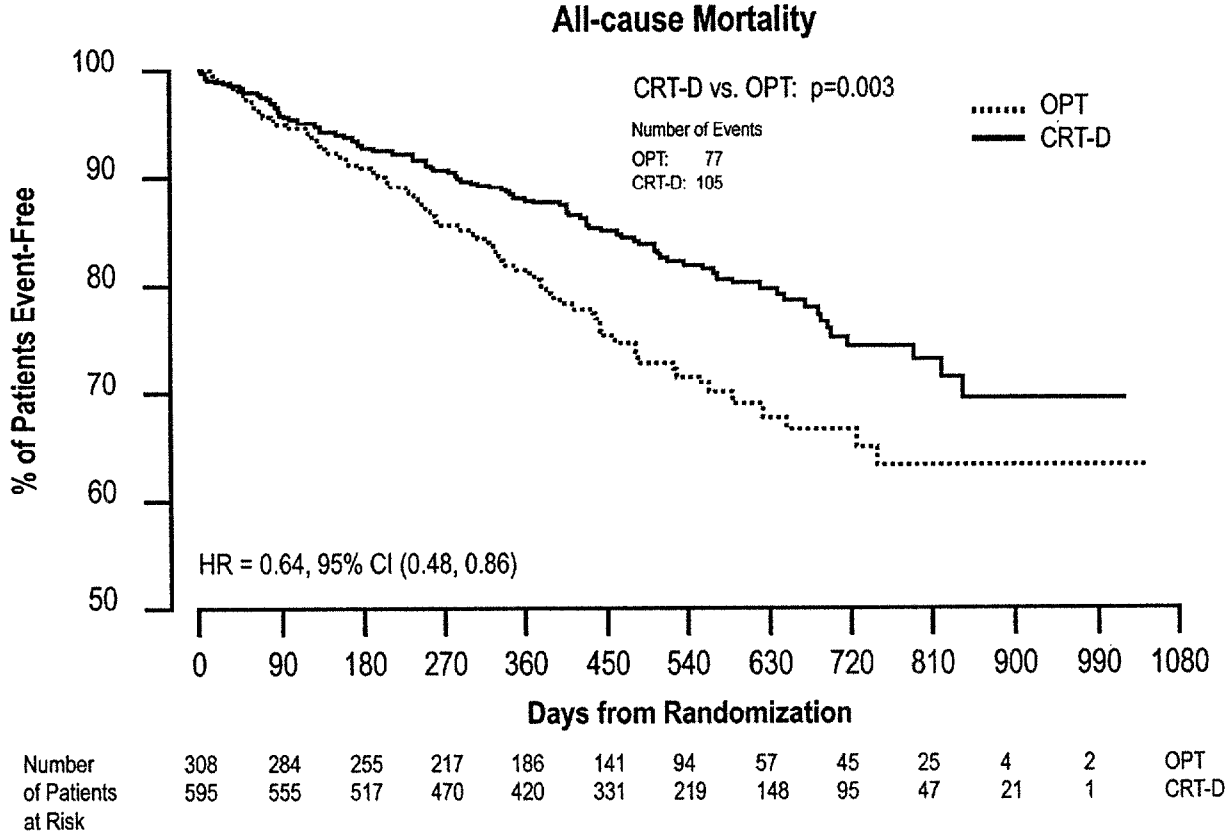
	% Failure		Absolute Risk Reduction	Relative Risk Reduction
	OPT	CRT-D		
6 months	44.9% (38.9%, 50.3%)	42.9%(38.7%, 46.7%)	2.0%	4.5%
12 months	68.0% (61.7%, 73.2%)	55.9% (51.6%, 59.8%)	12.1%	17.8%
18 months	77.8% (71.6%, 82.7%)	69.0% (64.5%, 73.1%)	8.8%	11.3%

11.6.2 SECONDARY ENDPOINTS

11.6.2.1 ALL-CAUSE MORTALITY

Deaths from any cause were reported in 77 patients randomized to OPT and 105 patients randomized to CRT-D (p = 0.003, p = 0.004 after adjusting for interim analyses). The Kaplan-Meier curves are depicted in Figure 5. These numbers correspond to an annual mortality rate of 19% in the OPT arm and 12% in the CRT-D arm, with a hazard ratio of 0.64, 95% CI (0.48, 0.86). These results demonstrated that CRT-D was associated with a 36% relative reduction in the risk of all-cause mortality when compared to OPT alone.

Figure 5: Secondary Endpoint: All-cause Mortality



In addition to the hazard ratio, point estimates of risk reduction were also calculated (Table 8). These estimates will vary with time from the true treatment effect, and thus should be interpreted with caution.

Table 8: Mortality Endpoint Risk Reduction Point Estimates
(Overall Hazard Ratio = 0.64; p = 0.003)

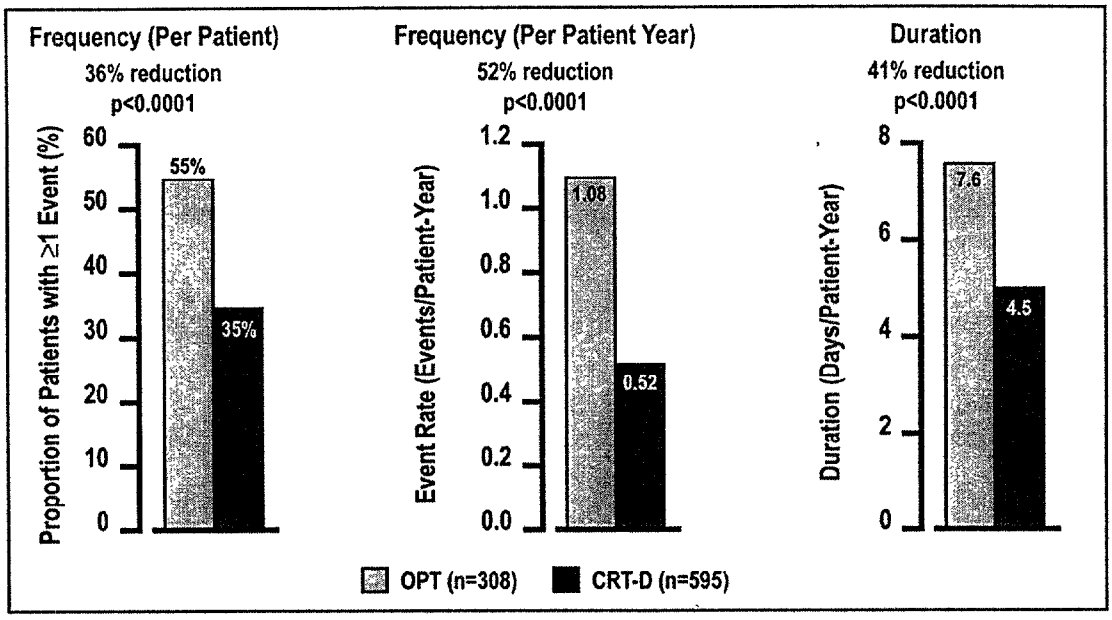
	% Failure		Absolute Risk Reduction	Relative Risk Reduction
	OPT	CRT-D		
6 months	9.0% (5.7%, 12.2%)	7.3% (5.1%, 9.3%)	1.7%	18.9%
12 months	18.9% (14.1%, 23.5%)	12.1% (9.3%, 14.8%)	6.8%	36.0%
18 months	28.4% (22.3%, 34.1%)	18.0% (14.4%, 21.5%)	10.4%	36.6%

11.6.2.2 CARDIAC MORBIDITY

Cardiac morbid events were reported during hospitalizations. During a hospitalization more than one of the pre-specified cardiac morbid events could occur. The Anderson-Gill extension to the Cox proportional hazard model was used to analyze time to multiple cardiac morbid events. Caution must be used in interpreting p-values in this analysis because this analysis does not account for the competing risk of death.

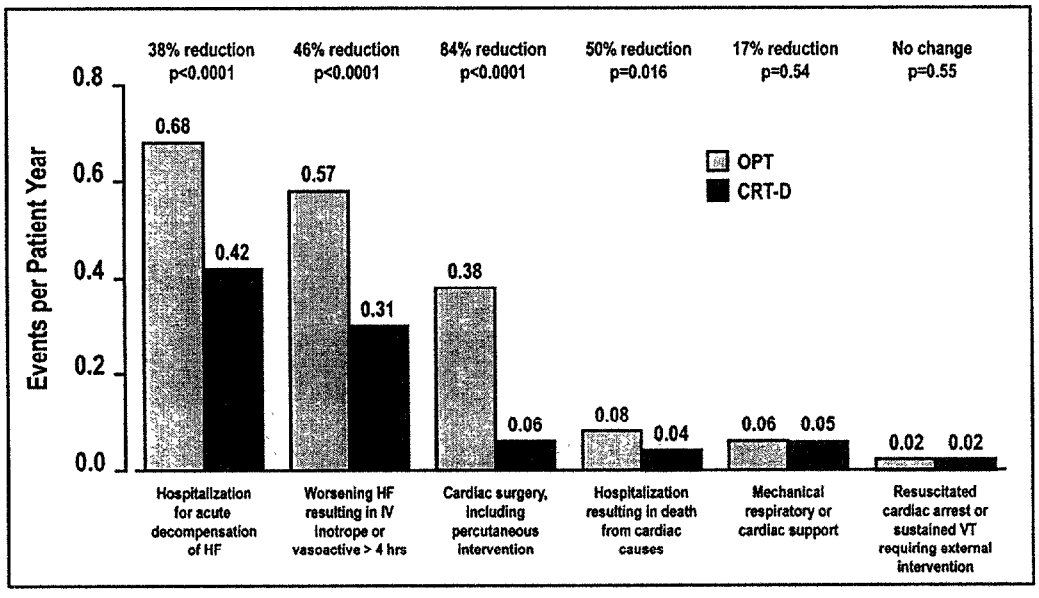
In Figure 6, the frequency and duration of cardiac morbid events are illustrated. CRT-D was associated with a 36% reduction ($p < 0.0001$) in the proportion of patients with at least one event, a 52% reduction ($p < 0.0001$) in events on an annual basis, and a 41% reduction ($p < 0.0001$) in the hospital duration on an annual basis. These reductions are primarily due to the reduction of hospitalizations for acute decompensation of heart failure, worsening heart failure resulting in IV inotrope or vasoactive therapy > 4 hours (during an inpatient hospitalization) and cardiac surgery (including percutaneous intervention), as shown in Figure 7.

Figure 6: Secondary Endpoint of Cardiac Morbidity.



Caution must be used in interpreting p-values; analysis does not account for competing risk of death.

Figure 7: Cardiac Morbidity by Major Component.



Note: For a given cardiac hospitalization, patients may have events in more than one category and only the first event in each category was counted.

11.6.3 IMPLANT DISPOSITION

Table 9 identifies the number of initial and subsequent implant procedures attempted in patients randomized to CRT-D and the rate of success for each additional implant procedure. There were 81 CRT-D patients that had an unsuccessful initial implant for the CRT-D system. Fifty (50) of these patients had a second implant procedure, of which 33 were successful and 17 were unsuccessful. Three patients had a third implant procedure, of which one was successful. Therefore, there were 541 patients implanted with the CRT-D system.

Table 9: CRT-D System Implant Disposition

		Attempt successful	Failed implant	Reattempt not done after this procedure
Initial implants	588 (98.8%)	507 (85.0%)	81 (14.0%)	31 (5.2%)
First reattempt	50 (8.4%)	33 (5.5%)	17 (2.9%)	14 (2.3%)
Second reattempt	3 (0.5%)	1 (0.2%)	2 (0.3%)	2 (0.34%)

11.6.4 ADDITIONAL OUTCOME MEASURES

11.6.4.1 FIRST HEART FAILURE HOSPITALIZATIONS

An additional outcome that was not pre-specified in the protocol provides further insight into the results observed in the composite primary endpoint. This post-hoc analysis was conducted using cause-specific hospitalizations as adjudicated by the morbidity and mortality committee and therefore should be interpreted with caution.

The outcome of all-cause mortality or first heart failure hospitalization was analyzed on an intention-to-treat basis and time to first event.

Hospitalizations were defined per the following:

- Care provided at a hospital for any reason in which the duration is associated with a date change, or
- Use of intravenous inotropes and/or vasoactive drugs for a duration > 4 hours (inpatient or outpatient).

NOTE: Hospitalizations associated with a device implant attempt or re-attempt are excluded.

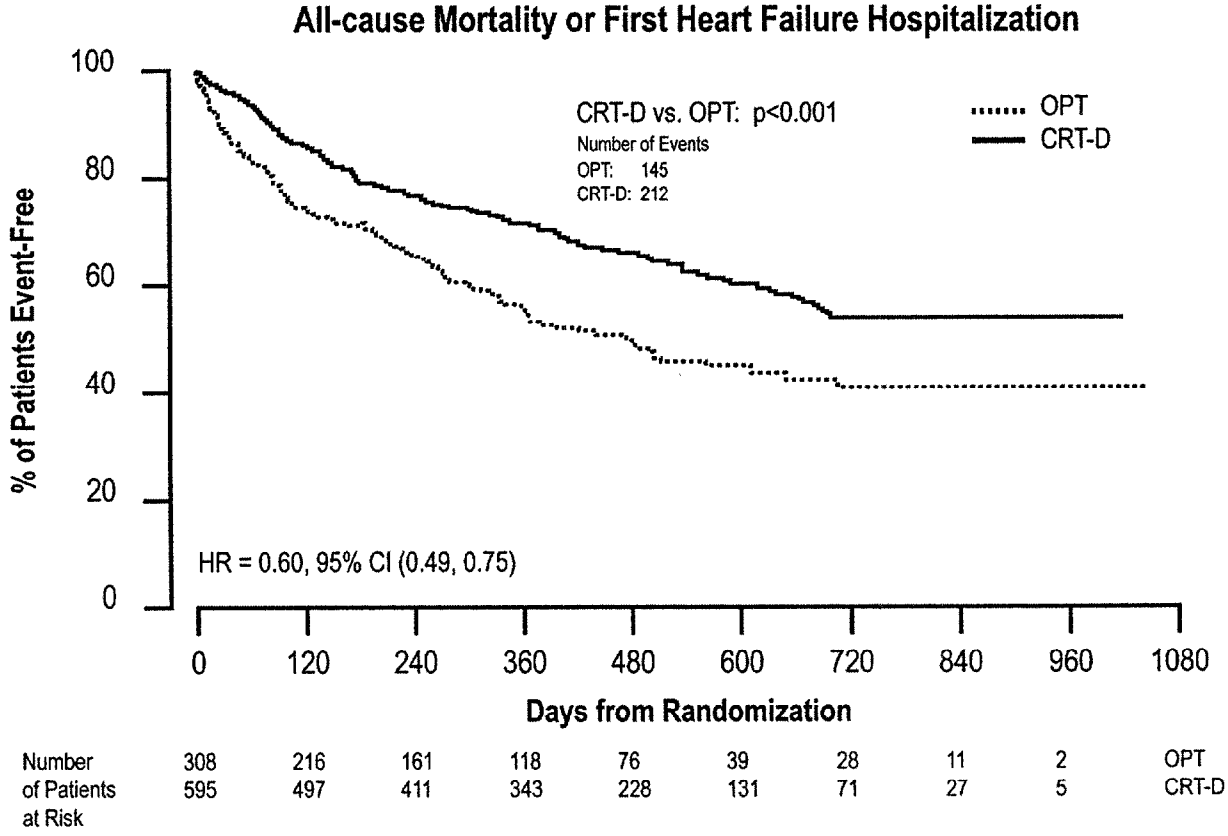
Those contributing to the heart failure hospitalization outcome were required by the Morbidity and Mortality committee to meet at least one of the following additional criteria:

- IV diuretics
- IV inotrope/vasoactive therapy
- Other parenteral therapy for the treatment of heart failure
- Significant alterations in oral therapy for the treatment of heart failure

11.6.4.2 ALL-CAUSE MORTALITY OR FIRST HEART FAILURE HOSPITALIZATION

The Kaplan-Meier curves for all-cause mortality or first heart failure hospitalization is shown in Figure 8. OPT and CRT-D had annual event rates of 45% and 29%, respectively with a hazard ratio of 0.60, 95% CI (0.49-0.75), $p < 0.001$. Therefore, CRT-D was associated with a 40% relative reduction in the risk of all-cause mortality or first heart-failure hospitalization when compared to OPT alone.

Figure 8: Additional Outcome: All-cause Mortality or First Heart Failure Hospitalization.



11.6.4.3 DISPOSITION OF HOSPITALIZATION

Implantation of the CRT-D system generally requires hospitalization. To differentiate between the hospitalization required to implant the system and those hospitalizations that occurred after the system was implanted, the following terms are used:

Implant hospitalization: The elective hospitalization associated with either the implant procedure or a repeat implant procedure if the initial procedure was unsuccessful.

All other hospitalizations: Patients who required a revision for an implanted system (e.g., lead dislodgment or infection) were included in this category as were hospitalizations for non-elective device related implants.

The hospitalizations analysis illustrated in Figure 9 and hospitalization days analysis in Figure 10 depicts hospitalization data stratified by implant and non-elective hospitalizations. This analysis was on an intention-to-treat basis and includes patients who underwent an attempted implant procedure. Patients randomized to CRT-D had a follow-up duration approximately 30% longer than OPT patients. Thus, hospitalization data are normalized per patient-year of follow-up. An additional comparison of hospitalization days for heart failure hospitalizations is shown in Figure 11.

NOTE: CRT-D was associated with a reduction in all-cause mortality and therefore there is a competing risk for hospitalizations. This data should be interpreted with caution.

Figure 9: Hospitalizations/Patient year

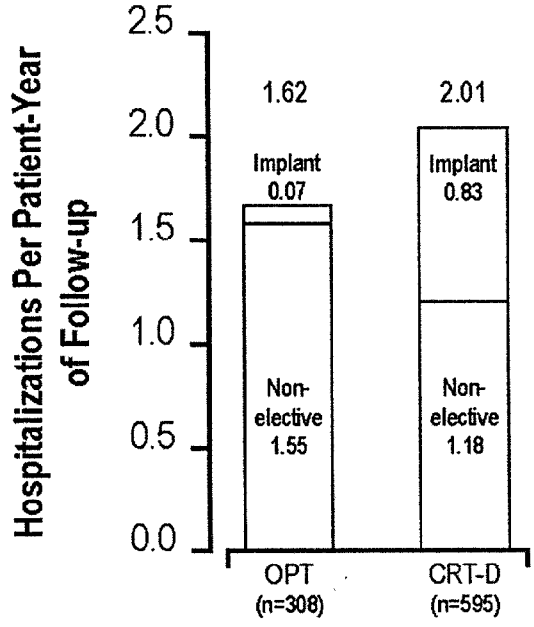


Figure 10: Hospitalization Days/Patient-Year

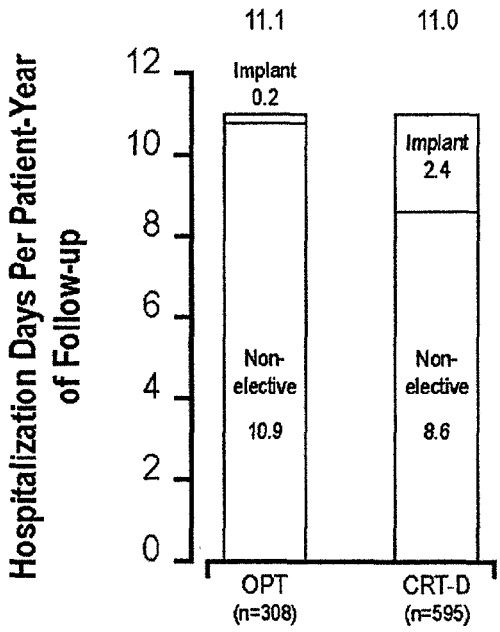
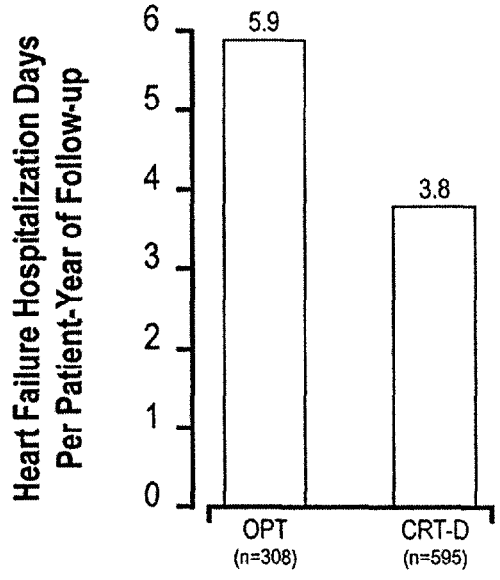


Figure 11: Heart Failure Hospitalization Days/Patient-Year



11.6.4.4 CRT-D System Safety

The system-related complication-free rate analysis was not a predefined endpoint in the protocol. The intent of this analysis is to provide reasonable assurance of safety of the CONTAK CD system in this patient population. The system-related complication-free rate was defined over a six-month follow-up period as the proportion of patients who are free of complications attributed to:

- Any implanted component (e.g, pulse generator, coronary venous lead, right atrial pace/sense lead, cardioversion/defibrillation lead)
- The surgical procedure required to implant the CRT-D system

In the COMPANION study, this analysis was performed on an intention-to-treat basis and also extends to those patients who underwent an implant procedure but did not ultimately receive a device. Of the 595 patients analyzed, 522 (87.7%) were free of system-related complications.

Of the 73 (12.3%) patients who experienced a system-related complication, the most common were loss of left ventricular capture (25 patients, 4.2%), loss of right atrial capture (9 patients, 1.5%), and phrenic nerve/ diaphragmatic stimulation (8 patients, 1.3%).

When analyzed on a time-to-event basis, the system-related complication-free rate was 87.7%. The safety performance of the CONTAK CD system compares favorably with the safety performance observed in the prior CONTAK CD study (P010012, May 2, 2002).

11.6.5 Additional Functional Capacity Data

In addition to the Exercise Performance sub-study[12], functional capacity was evaluated by means of NYHA Class, six-minute walk distance, and Minnesota Living with Heart Failure Questionnaire© QOL for the all patients in COMPANION randomized to OPT and CRT-D through 6-months of follow up.

As shown in Table 10, NYHA Class, six-minute walk distance, and QOL scores were improved in the CRT-D group compared to the OPT group at 3 and 6 months. These findings are similar to those presented in the exercise performance sub-study and previous cardiac resynchronization therapy trials.

[12] The exercise performance substudy was reviewed previously (P030005, approved January 26, 2004, http://www.fda.gov/cdrh/pdf3/p030005.html) and is not discussed in detail in this document.

Table 10: Changes in Six-Minute Walk, QOL and NYHA

	CRT-D		OPT		P-value[a]
Six Minute Walk Distance	N	Mean ± SD	N	Mean ± SD	
Δ at 3 months	420	42 ± 98	172	8 ± 82	< 0.0001
Δ at 6 months	377	45 ± 98	141	2 ± 92	< 0.0001
QOL	N	Mean ± SD	N	Mean ± SD	
Δ at 3 months	514	-24 ± 28	243	-8 ± 21	< 0.0001
Δ at 6 months	479	-23 ± 28	207	-12 ± 23	< 0.0001
NYHA	N	% Improved	N	% Improved	
Δ at 3 months	543	55	242	24	< 0.0001
Δ at 6 months	498	57	199	38	< 0.0001

* P-values are not adjusted for multiplicity and were obtained using t-tests for continuous data and chi-square for categorical data.

12 COMPANION TRIAL CONCLUSIONS

It is reasonable to conclude based on the COMPANION results that the benefits of use of Guidant's CRT-D devices for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

The COMPANION trial results for the combined primary endpoint of all-cause mortality or first hospitalization demonstrate that heart failure patients implanted with CRT-D in addition to OPT have a significant reduction in all-cause mortality or first hospitalization compared to heart failure patients treated with OPT alone. The results of the all-cause mortality endpoint demonstrate that heart failure patients implanted with CRT-D in addition to OPT have a significant reduction in mortality compared to heart failure patients treated with OPT alone. In addition, the safety performance of the CONTAK CD system in the COMPANION trial compared favorably with the safety performance observed in the prior CONTAK CD study[13].

13 PANEL RECOMMENDATION

On July 28, 2004, the Circulatory System Devices Panel met to review the sponsor's request for approval of an expanded indication and new claims based on the results from the COMPANION clinical trial. The Panel recommended that the PMA supplement be approved and the sponsor's CRT-D indication be expanded to include the entire patient population defined by the COMPANION enrollment criteria with the following conditions:

- The Indications for Use should be amended to remove the language referring to "all-cause hospitalization" (part of the composite primary endpoint) and

[13] P010012, approved May 2, 2002, http://www.fda.gov/cdrh/pdf/P010012.html

simply refer to the secondary endpoint of all-cause mortality and improvement in symptoms.

- The labeling should include a separate statement about the hospitalization experience in the clinical trial, along with the appropriate explanatory language and caveats that capture the Panel's concerns.

The first condition described above reflected the concern expressed by the Panel regarding the fact that the definition of hospitalization used for evaluation of the primary endpoint was modified during the course of the trial. However, the Panel recommmended that the primary and secondary endpoint results be characterized in the clinical section of the device labeling. The second condition reflected the concern that the primary endpoint, which was a time-to-first-event analysis, would not adequately characterize hospitalization, which is a reccuring event.

The Panel also recommended that data obtained from patients who were re-consented after withdrawal be used in the analyses of the primary and secondary endpoints in order to account for the large withdrawal rate of patients in the OPT arm of the trial.

14 CDRH DECISION

FDA's review of the COMPANION trial raised several critical concerns regarding how the trial was conducted and how the data were subsequently analyzed. Recommendations provided to FDA by the Circulatory System Devices Panel were useful in determining how results from the COMPANION trial should impact the sponsor's CRT-D indication and how these results should be presented in the device labeling. The Panel's recommendations were implemented and resulted in changes to the sponsor's CRT-D indication and device labeling.

As suggested by the Panel, the final indication for the sponsor's CRT-D devices describes an expanded patient population defined by the COMPANION enrollment criteria. The CRT-D labeling was modified to characterize a mortality benefit as well as a benefit in the primary composite endpoint.

FDA agreed with the panel's concerns regarding changes to the definition of the primary endpoint that occurred during the trial. While these changes raise some concerns regarding the integrity of the primary endpoint result, FDA determined that the endpoint should be described in the sponsor's CRT-D labeling for several reasons: 1) The final definition of the endpoint is clinically meaningful; 2) FDA believes that few meaningful hospitalizations were missed using the final definition; and 3) The definition appears to have been changed by the Morbidity and Mortality Committee without knowledge of any results. The panel's recommendation that the primary endpoint not be referenced in the Indication for Use statement was followed. While the panel suggested that the Indication for Use should characterize the mortality and heart failure symptoms benefit, FDA determined that, in accordance with 21 CFR 814.20(b)(3)(i), expected clinical outcomes should be described in a separate section.

Therefore, a Clinical Outcomes section was added to the labeling to characterize expected patient outcomes based on the COMPANION trial results.

As recommended by the panel, the CRT-D labeling was modified to more accurately and thoroughly characterize hospitalizations and adverse events. In addition, as recommended by the panel, data obtained from patients who were re-consented after withdrawal were used in the analyses of the primary and secondary endpoints in order to account for the large withdrawal rate of patients in the OPT arm of the trial.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820). This submission (P010012/S026) was granted expedited review status on March 29, 2004 because, at the time, no legally marketed cardiac resynchronization and defibrillation device was available to the entire COMPANION population. FDA issued an approval order for P010012/S026 on September 14, 2004.

15 APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.